Pre-clinical radiotherapy

Social impact and valorisation

1. Relevance: societal impact

Cancer is a leading cause of mortality and morbidity worldwide: one in five men and one in six women develop cancer during their lifetime [GLOBOCAN, 2018]. The affected population can be much higher if besides the patient, the family and social circle are considered to be dealing with the disease. The main therapy options consist of surgery, chemotherapy, radiotherapy or combination strategies. For many cancer types, such strategies succeed in prolonging life, but survival remains poor due to disease relapses and treatment failure. Radiotherapy, the focus of this thesis, aims to deliver a sufficiently high dose of ionizing radiation to the tumour while sparing surrounding healthy tissues as much as possible. Chapter 1 describes how, historically, therapies evolved in an urgent fashion: as novel treatment strategies were critical, they were not always based on randomized clinical trials, biological models or epidemiological studies and, currently, as technology evolves swiftly and yields probable patient benefit, the shift towards sophisticated conformal therapies has also not been thoroughly validated on animal models or human trials.

In this scenario, pre-clinical research platforms provide a cost-effective experimental pipeline for timely validation of new treatment modalities or interpretation of clinical experience on large cohorts. This link is essential for innovation in cancer care and to unravel fundamental questions of radiotherapy, thus, directly impacting a vast fraction of the society. Investing on high quality pre-clinical radiotherapy amplifies research scope, minimizes study costs, animal usage and increases the likelihood of clinical translation.

2. Products and innovation

In this thesis different strategies for increasing quality and value of pre-clinical radiotherapy were shown.

Imaging

Imaging is pivotal in radiotherapy as treatment plans are developed based on information retrieved from CT scans. Particular to small animal irradiation is the requirement for decreased spatial resolution due to size of the specimens investigated. Our group pioneered the development of dual-energy CT techniques for pre-clinical radiotherapy. A simple and effective method to retrieve atomic composition from CT images was developed and thus generated another layer of information on top of the regular tissue densities present on CT scans. Throughout this thesis the added value of this technique resonates: it improves tissue segmentation, decreases dose calculation errors and ultimately helps to ensure that the simulation and treatment doses coincide. The latter is a crucial point as the translation of research to the clinic is dependent on precise irradiation regimens.

A software platform for pre-clinical cone-beam CT image reconstruction using analytical and iterative techniques is an important product of this research. This software has been developed based on open-source libraries and published algorithms. While commercial solutions provide only limited analytical reconstruction software prone to noise and artefacts, our platform allows for image reconstruction using different algorithms, filters, artefact reduction kernels and it is likely to produce images of superior quality. The software can potentially be distributed or commercialized among other small animal irradiator users and contribute to improving image quality throughout this field.

Irradiation

A tool for defining optimal irradiation collimators for lung tumours is another product of this research. Software was developed to determine irradiation margins, based on the specimen breathing function and the available collimators of the machine. Although the concept of irradiation margins is essential for clinical radiotherapy, in the pre-clinical field it is still incipient. This was the first research to challenge this concept and propose a solution in the shape of a recipe, considering anatomy and hardware. As this research was first presented at the 4th Conference on Small Animal Precision Image-Guided Radiotherapy, in Lisbon, 2018, it was awarded a prize, which is an important measurement for its relevance.

A contribution has been given to the light ion field, following the great expansion of this radiotherapy technique in the Netherlands and worldwide. Although proton therapy can potentially decrease short and long term secondary effects of radiation in the human body there is still little evidence favouring proton in comparison to photon therapy. As building costs for dedicated research facilities are prohibitive, the adaptation of a clinical set-up for pre-clinical irradiation was investigated and proved feasible within very short irradiation times. This is an important result as it enables research on biological effects of proton beams, comparison between treatment strategies and adjuvant therapies, development of new imaging modalities and gathering of evidence regarding the benefits of this technique.

Dose concept

A final contribution of this research challenges differences between analytical dose calculation algorithms (clinically and pre-clinically available), Monte Carlo techniques and the concept of dose to water and dose to medium. Using the two quantities, for kilovolt energies, large dose differences were found for tissues which differ from water in terms of elemental compositions e.g. adipose and bone. Because the different calculation methods coexist in practice and for the last two decades the scientific community has not agreed on which quantity should prevail, this research brings evidence to pursue in-vivo experiments as ultimately one dose quantity brings a higher biological damage. This research has a direct clinical effect as worldwide thousands of patients are treated daily with kilovolt treatments.

3. Market & target groups

The last decennium saw the rise of two pre-clinical radiation research cabinet vendors, Precision X-Ray Inc (USA) and XStrahl ltd (UK), which brought unprecedented image guidance and enabled precise animal irradiation. Currently, there are over 130 irradiators from both companies worldwide, each of which may cost well above half a million euros. Despite the lavish prices, these irradiators were not initially supplied with commercial software, forcing users to limit their potential scope or to invest in in-house solutions. Thus, in parallel, a spin-off company was established to act on these shortcomings, providing solutions to users of different backgrounds, e.g. SmART Scientific Solutions BV (Maastricht, the Netherlands), and have since expanded their sphere of influence. Lastly, partially due to the expansion of pharmaceutical and clinical research organizations into the pre-clinical field, imaging modalities with a clinical analogue e.g. MRI, CT, PET, SPECT, optical fluorescence or modalities unique to pre-clinical studies e.g. optical bioluminescence, intravital microscopy and phase contrast optical imaging have incorporated the most recent advances in technology to e.g. provide sub-millimetre resolution and quantification. The cost associated with these techniques can range from tens of thousands for fluoroscopy to over a million for a state-of-the-art MRI facility. The small animal imaging market is estimated to reach 2.5 billion dollars by 2025 [source: iHealthcareAnalyst, Inc., Sep. 9, 2019].

The pre-clinical market is in expansion which increasingly affects different medical and pharmaceutical fields. On the irradiation side, so far, research has mainly focused on radiation therapy for cancer treatment using photons. It is a broad field which continuously absorbs new technologies and requires experimenting to unfold underlying physical, chemical and biological mechanisms. The irradiators are also a platform for research on radiation as a therapy agent for diseases other than cancer, such as brain malformations, epilepsy, aneurysm and regenerative medicine and, in the pharmaceutical field, to test the benefit of agents from chemotherapy, immunotherapy, gene therapy or targeted therapy in combination with or compared to radiotherapy. The imaging segment is an invaluable component of modern biomedical research due to its clinically translatable, non-invasive and quantitative nature. It provides means of serially assaying biological structure and function, from oncological (or cardiovascular, neurological, etc.) disease inception to progression, and monitoring treatment effectiveness. It is employed in several fields, for treatment monitoring, novel therapeutic strategies evaluation and drug development. Quantitative imaging is likely to accelerate drug discovery and provide earlier and more clinically meaningful assays of therapeutic response, thereby avoiding unnecessary toxicities, expense and loss of time.

As photon irradiation may not be the ideal option for many cases, there are ongoing major investments into proton and ion irradiation clinical treatment centres. In July 2019, there were 162 particle therapy facilities worldwide (44 under construction, 23 planned and 95 operational), however very few pre-clinical commercial (or in-house) solutions. This field requires extensive pre-clinical investigation to prove and promote the added benefit of particle therapy thus, it is expected to present substantial growth in the next decade.